Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies.

Bibliographic Source(s)

Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Heart Rhythm. 2011 Aug;8(8):1308-39. [278 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The class of recommendation (I, IIa, IIb, and III) and level of evidence (C) are defined at the end of the "Major Recommendations" field.

All recommendations are level of evidence C (i.e., based on experts' opinions).

Introduction

1. Genetic counseling is recommended for all patients and relatives with the familial heart diseases detailed in the original consensus document and should include discussion of the risks, benefits, and options available for clinical testing and/or genetic testing.
2. Treatment decisions should not rely solely on his/her genetic test result but should be based on an individual's comprehensive clinical evaluation.
3. It can be useful for pre-genetic test counseling, genetic testing, and the interpretation of genetic test results to be performed in centers experienced in the genetic evaluation and family-based management of the heritable arrhythmia syndromes and cardiomyopathies described in this document.

State of Genetic Testing for Long QT Syndrome (LQTS)

1. Comprehensive or LQT1-3 (*KCNQ1*, *KCNH2*, and *SCN5A*) targeted LQTS genetic testing is recommended for any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead electrocardiograms [ECGs] and/or provocative stress testing with exercise or catecholamine infusion) phenotype. (Class I)

2. Comprehensive or LQT1-3 (*KCNQ1*, *KCNH2*, and *SCN5A*) targeted LQTS genetic testing is recommended for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, bundle branch block, etc., i.e., otherwise idiopathic) on serial 12-lead ECGs defined as QTc >480 ms (prepuberty) or >500 ms (adults). (Class I)
3. Comprehensive or LQT1-3 (*KCNQ1*, *KCNH2*, and *SCN5A*) targeted LQTS genetic testing may be considered for any asymptomatic patient with otherwise idiopathic QTc values >460 ms (prepuberty) or >480 ms (adults) on serial 12-lead ECGs. (Class IIb)
4. Mutation-specific genetic testing is recommended for family members and other appropriate relatives subsequently following the identification of the LQTS-causative mutation in an index case. (Class I)

State of Genetic Testing for Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

1. Comprehensive or CPVT1 and CVPT2 (*RYR2* and *CASQ2*) targeted CPVT genetic testing is recommended for any patient in whom a cardiologist has established a clinical index of suspicion for CPVT based on examination of the patient's clinical history, family history, and expressed electrocardiographic phenotype during provocative stress testing with cycle, treadmill, or catecholamine infusion. (Class I)
2. Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the CPVT-causative mutation in an index case. (Class I)

State of Genetic Testing for Brugada Syndrome (BrS)

1. Comprehensive or BrS1 (*SCN5A*) targeted BrS genetic testing can be useful for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype. (Class IIa)
2. Genetic testing is not indicated in the setting of an isolated type 2 or type 3 Brugada ECG pattern. (Class III)
3. Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case. (Class I)

State of Genetic Testing for Progressive Cardiac Conduction Disease (CDD)

1. Genetic testing may be considered as part of the diagnostic evaluation for patients with either isolated CCD or CCD with concomitant congenital heart disease, especially when there is documentation of a positive family history of CCD. (Class IIb)
2. Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the CCD-causative mutation in an index case. (Class I)

State of Genetic Testing for Short QT Syndrome (SQTS)

1. Comprehensive or SQT1-3 (*KCNH2*, *KCNQ1*, and *KCNJ2*) targeted SQTS genetic testing may be considered for any patient in whom a cardiologist has established a strong clinical index of suspicion for SQTS based on examination of the patient's clinical history, family history, and electrocardiographic phenotype. (Class IIb)
2. Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the SQTS-causative mutation in an index case. (Class I)

State of Genetic Testing for Atrial Fibrillation (AF)

1. Genetic testing is not indicated for atrial fibrillation at this time. (Class III)
2. Single nucleotide polymorphism (SNP) genotyping in general and SNP rs2200733 genotyping at the 4q25 locus for AF is not indicated at this time based on the limited outcome data currently available. (Class III)

State of Genetic Testing for Hypertrophic Cardiomyopathy (HCM)

1. Comprehensive or targeted (*MYBPC3*, *MYH7*, *TNNI3*, *TNNT2*, *TPMI*) HCM genetic testing is recommended for any patient in whom a cardiologist has established a clinical diagnosis of HCM based on examination of the patient's clinical history, family history, and electrocardiographic/echocardiographic phenotype. (Class I)
2. Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the HCM-causative mutation in an index case. (Class I)

State of Genetic Testing for Arrhythmogenic Cardiomyopathy (ACM)/Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

1. Comprehensive or targeted (*DSC2*, *DSG2*, *DSP*, *JUP*, *PKP2*, and *TMEM43*) ACM/ARVC genetic testing can be useful for patients satisfying task force diagnostic criteria for ACM/ARVC. (Class IIa)

2. Genetic testing may be considered for patients with possible ACM/ARVC (1 major or 2 minor criteria) according to the 2010 task force criteria. (Class IIb)
3. Genetic testing is not recommended for patients with only a single minor criterion according to the 2010 task force criteria. (Class III)
4. Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of the ACM/ARVC-causative mutation in an index case. (Class I)

State of Genetic Testing for Dilated Cardiomyopathy (DCM)

1. Comprehensive or targeted (*LMNA* and *SCN5A*) DCM genetic testing is recommended for patients with DCM and significant cardiac conduction disease (i.e., first, second, or third-degree heart block) and/or a family history of premature unexpected sudden death. (Class I)
2. Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, to recognize those who are at highest risk of arrhythmia and syndromic features, to facilitate cascade screening within the family, and to help with family planning. (Class IIa)
3. Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of a DCM-causative mutation in the index case. (Class I)

State of Genetic Testing for Left Ventricular Noncompaction (LVNC)

1. LVNC genetic testing can be useful for patients in whom a cardiologist has established a clinical diagnosis of LVNC based on examination of the patient's clinical history, family history, and electrocardiographic/echocardiographic phenotype. (Class IIa)
2. Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of an LVNC-causative mutation in the index case. (Class I)

State of Genetic Testing for Restrictive Cardiomyopathy (RCM)

1. RCM genetic testing may be considered for patients in whom a cardiologist has established a clinical index of suspicion for RCM based on examination of the patient's clinical history, family history, and electrocardiographic/echocardiographic phenotype. (Class IIb)
2. Mutation-specific genetic testing is recommended for family members and appropriate relatives following the identification of an RCM-causative mutation in the index case. (Class I)

State of Genetic Testing for Out-of-Hospital Cardiac Arrest Survivors

1. In the survivor of an unexplained out-of-hospital cardiac arrest, genetic testing should be guided by the results of medical evaluation and is used for the primary purpose of screening at-risk family members for subclinical disease. (Class I)
2. Routine genetic testing, in the absence of a clinical index of suspicion for a specific cardiomyopathy or channelopathy, is not indicated for the survivor of an unexplained out-of-hospital cardiac arrest. (Class III)

State of Post-mortem Genetic Testing in Sudden Unexplained Death (SUD) Cases (SUD/Sudden Infant Death Syndrome [SIDS])

1. For all SUDS and SIDS cases, collection of a tissue sample is recommended (5–10 mL whole blood in ethylenediaminetetraacetic acid [EDTA] tube, blood spot card, or a frozen sample of heart, liver, or spleen) for subsequent deoxyribonucleic acid (DNA) analysis/genetic testing. (Class I)
2. In the setting of autopsy-negative SUDS, comprehensive or targeted (*RYR2*, *KCNQ1*, *KCNH2*, and *SCN5A*) ion channel genetic testing may be considered in an attempt to establish probable cause and manner of death and to facilitate the identification of potentially at-risk relatives and is recommended if circumstantial evidence points toward a clinical diagnosis of LQTS or CPVT specifically (such as emotional stress, acoustic trigger, drowning as the trigger of death). (Class IIb)
3. Mutation-specific genetic testing is recommended for family members and other appropriate relatives following the identification of a SUDS-causative mutation in the decedent. (Class I)

Definitions:

Class of Recommendation for Testing in Index Cases

Class I: "Is recommended." Applied for genetic testing in index cases with a sound clinical suspicion for the presence of a channelopathy or a cardiomyopathy when the positive predictive value of a genetic test is high (likelihood of positive result >40% and signal/noise ratio >10; see Table 3 in the original consensus document), AND/OR when the genetic test result provides either diagnostic or prognostic information, or when the genetic test result influences therapeutic choices according to data in Figure 1 and in Table 3 in the original consensus document.

Class IIa: "Can be useful."

Class IIb: "May be considered."

Class III: "Should not" or "is not recommended." Applied in cases in which it was agreed that the genetic test result failed to provide any additional benefit or could be harmful in the diagnostic evaluation of patients with possible inherited heart disease.

Class of Recommendation for Testing in Family Members of the Proband

Class I: Genetic testing leads to the adoption of therapy/protective measures/lifestyle adaptations.

Class IIa: Results of genetic testing are not associated with the use of therapeutic or protective measures but the results may be useful for reproductive counseling or instances in which genetic testing is requested by the patient who wants to know his/her mutation status.

Level of Evidence

Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses.

Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies.

Level of Evidence C: Only consensus opinion of experts.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Heritable channelopathies and cardiomyopathies, including:

- Long QT syndrome
- Catecholaminergic polymorphic ventricular tachycardia
- Brugada syndrome
- Progressive cardiac conduction disease
- Short QT syndrome
- Atrial fibrillation
- Hypertrophic cardiomyopathy
- Arrhythmogenic cardiomyopathy/arrhythmogenic right ventricular cardiomyopathy
- Dilated cardiomyopathy
- Left ventricular noncompaction
- Restrictive cardiomyopathy
- Out-of-hospital cardiac arrest
- Sudden unexpected death/sudden infant death syndrome (SUD/SIDS)

Guideline Category

Counseling

Diagnosis

Evaluation

Prevention

Risk Assessment

Clinical Specialty

Cardiology

Medical Genetics

Pediatrics

Preventive Medicine

Psychology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Guideline Objective(s)

- To provide the state of genetic testing for the channelopathies and cardiomyopathies
- To summarize the opinion of the international writing group members with respect to the use and role of genetic testing for these potentially heritable cardiac conditions

Target Population

Patients with channelopathies and cardiomyopathies and their families

Interventions and Practices Considered

1. Genetic counseling for all patients and relatives with the familial heart disease
2. Examination of the patient's clinical history, family history, and expressed electrocardiographic/echocardiographic phenotype
3. Comprehensive genetic testing
4. Targeted genetic testing
5. Mutation-specific genetic testing
6. Post-mortem genetic testing in sudden unexpected death cases (SUD/SIDS)

Major Outcomes Considered

- Sensitivity, positive predictive value, yield, and false negative rates of genetic tests
- Signal-to-noise ratio of genetic tests
- Likelihood that a genetic test will provide diagnostic or prognostic information
- Likelihood that a genetic test will influence therapeutic choices or adoption of protective measures or lifestyle adaptations
- Likelihood that a genetic test will be harmful in diagnostic evaluation
- Likelihood that a genetic test will be useful for reproductive counseling
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The Medline and PubMed databases were searched. An initial literature search was performed in December of 2009 at the time the document writing committee was initiated. Subsequent literature searches were performed as needed throughout document development and concluded in May of 2011. All randomized and observational studies in humans were included in literature searches. Initial search terms of genetic testing and long QT, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, cardiac conduction disease, short QT syndrome, atrial fibrillation, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, dilated cardiomyopathy, cardiac conduction defect, left ventricular non-compaction, restrictive cardiomyopathy, sudden unexplained death syndrome, sudden infant death syndrome; each section author was responsible for adding search criteria relevant to their section.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Level of Evidence

Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses.

Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies.

Level of Evidence C: Only consensus opinion of experts.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

This international consensus statement summarizes the opinion of the international writing group members based on their own experience and on a general review of the literature with respect to the use and role of genetic testing for these potentially heritable cardiac conditions (channelopathies

and cardiomyopathies).

Writing recommendations for genetic diseases requires adaptation of the methodology normally adopted to prepare guidelines for clinical practice. Documents produced by other scientific societies have acknowledged the need to define the criteria used to rank the strength of recommendation for genetic diseases. The most obvious difference is that randomized and/or blinded studies do not exist. Instead, most of the available data are derived from registries that have followed patients and recorded outcome information. The authors of this statement have therefore defined specific criteria for Class I, Class IIa or b, and Class III recommendations and have used the conventional language adopted by the American Heart Association/American College of Cardiology/European College of Cardiology Guidelines to express each class (see the "Rating Scheme for the Strength of the Recommendations" field).

Recommendations are based on consensus of the writing group following the Heart Rhythm Society's established consensus process. It is recognized that consensus does not mean unanimous agreement among all writing group members. The writing group members identified those aspects of genetic testing for which a true consensus could be found. Surveys of the entire writing group were used. The authors received an agreement that was equal to or greater than 84% on all recommendations; most recommendations received agreement of 94% or higher.

Rating Scheme for the Strength of the Recommendations

Class of Recommendation for Testing in Index Cases

Class I: "Is recommended." Applied for genetic testing in index cases with a sound clinical suspicion for the presence of a channelopathy or a cardiomyopathy when the positive predictive value of a genetic test is high (likelihood of positive result >40% and signal/noise ratio >10; see Table 3 in the original consensus document), AND/OR when the genetic test result provides either diagnostic or prognostic information, or when the genetic test result influences therapeutic choices according to data in Figure 1 and in Table 3 in the original consensus document.

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Cost Analysis

Published cost analyses were reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

Not stated

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

All recommendations are level of evidence C (i.e., based on experts' opinions).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Appropriate use of genetic testing for the channelopathies and cardiomyopathies
- Refer to the original consensus document for diagnostic, prognostic, and therapeutic implications of specific genetic tests.

Potential Harms

- In genetic testing, many so-called "positive" test results are represented by less informative deoxyribonucleic acid (DNA) variants currently annotated with the expression "Variants of Uncertain Significance" (VUS). Only recently is the frequency of rare VUS among otherwise healthy volunteers across the exomes of various disease-causing genes being identified.
- The VUS issue and its associated possibility of a false positive genetic test results are also disease dependent, ranging from a relatively low rate of false positives for catecholaminergic polymorphic ventricular tachycardia (CPVT) testing to an alarmingly high rate of possible false positives associated with the arrhythmogenic cardiomyopathy (ACM)/arrhythmogenic right ventricular cardiomyopathy (ARVC) test. A false positive involves the identification of a rare but otherwise non-pathogenic mutation. For many disease-specific genetic tests, the false positive rate is unknown. The potential for false positive genetic test results rises significantly when genetic testing is pursued in settings in which the phenotype is ambiguous or absent, such as in screening. Consequently, there is no role for universal genetic testing for any of the diseases detailed in this statement. Instead, genetic testing must be phenotype directed. If the clinical diagnosis is in question, it may be prudent first to refer the patient to a center specializing in that particular disease rather than proceeding directly with genetic testing.

Qualifying Statements

Qualifying Statements

- When using or considering the guidance from this document, it is important to remember that there are no absolutes governing many clinical situations. The final judgment regarding care of a particular patient must be made by the health care provider and the patient in light of all relevant circumstances.
- The broader ethical, legal, and societal implications of genetic testing are beyond the scope of the original consensus document and a variety of national regulations and specifications exist.
- The genetic test result must be scrutinized with great caution, as all genetic tests are probabilistic tests rather than deterministic/binary ones. This issue of genetic test result interpretation applies to all the diseases detailed in the original consensus document.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Aug

Guideline Developer(s)

European Heart Rhythm Association - Professional Association

Heart Rhythm Society - Professional Association

Source(s) of Funding

Heart Rhythm Society

Guideline Committee

Writing Group

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Financial Disclosures/Conflicts of Interest

All members of this document-writing group provided disclosure statements of all relationships that might present real or perceptible conflicts of interest. Disclosures for the members of the task force are published in the Appendix section of the original consensus document.

Guideline Endorser(s)

American Heart Association - Professional Association

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the Heart Rhythm Society (HRS) Web site .

Availability of Companion Documents

The following is available:

- The HRS policy for development and endorsement of clinical guidance documents from HRS and others. Washington (DC): Heart Rhythm Society (HRS); 2009 Sep. 6 p. Available from the Heart Rhythm Society Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on February 13, 2013.

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